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COMPLETE SPECIFICATION

Improvements in or relating to Esters of α-Tocopherol

We, E. MERCK AKTIENGESELLSCHAFT, of Frankfurter Strasse 250, Darmstadt, Germany, a German Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a process for the production of esters of α-tocopherol and to the said α-tocopherol esters and their salts, which esters and salts are new compounds.

Free α-tocopherol is hardly used as a pharmaceutical preparation in view of its high sensitivity to oxidation. The material is used pharmaceutically in the form of an ester, the most popular form being the acetyl compound. Aliphatic esters of α-tocopherol, however, have the disadvantage that they are insoluble in water, a fact which leads to disadvantageous resorption conditions. This undesirable state of affairs has hitherto been remedied by esterification with polybasic acids, e.g. phosphoric or succinic acid, and converting into water soluble acid ester salts. This procedure, however, has had little success because the said polybasic acid esters are stable only in neutral or weakly alkaline solution. In the presence of acids, for example in the stomach or in acid cell medium, water insoluble acid esters are regenerated from the said acid ester salts.

The present invention consists in dialkylamino-acetic acid esters of α-tocopherol, of which each of the alkyl groups contains 1 or 2 carbon atoms.

The present invention also consists in physiologically acceptable salts of dialkylamino-acetic acid esters of α-tocopherol, of which each of the alkyl groups contains 1 or 2 carbon atoms; examples of these last mentioned salts are the hydrochlorides, hydrobromides, sulphates, citrates, phosphates and tartrates.

Specific compounds falling within the scope of the present invention are the dimethylamino-acetic acid ester of α-tocopherol; the diethylamino-acetic acid ester of α-tocopherol; the hydrobromide of the dimethylamino-acetic acid ester of α-tocopherol; the hydrochloride of the dimethylamino-acetic acid ester of α-tocopherol; the hydrochloride of the diethylamino-acetic acid ester of α-tocopherol; the hydrobromide of the diethylamino-acetic acid ester of α-tocopherol; the tartaric acid salt of the dimethylamino-acetic acid ester of α-tocopherol; the citric acid salt of the dimethylamino-acetic acid ester of α-tocopherol; the phosphoric acid salt of the dimethylamino-acetic acid ester of α-tocopherol; the sulphuric acid salt of the dimethylamino-acetic acid ester of α-tocopherol; the tartaric acid salt of the diethylamino-acetic acid ester of α-tocopherol; the citric acid salt of the diethylamino-acetic acid ester of α-tocopherol; the phosphoric acid salt of the diethylamino-acetic acid ester of α-tocopherol; the sulphuric acid salt of the diethylamino-acetic acid ester of α-tocopherol.

The salts with strong acids (which are strong acids in aqueous medium) of said new amino acid esters of α-tocopherol have, owing to the amphoteric character of the amino acid group, the advantage of being stable in a neutral or weakly acid medium and soluble therein.

The present invention further consists in a process for the production of dialkylamino-acetic acid esters of α-tocopherol, characterised in that α-tocopherol chloracetic acid ester is reacted, preferably at an elevated temperature, with a dialkylamine, e.g. containing 1 or 2 carbon atoms in each alkyl group, in the presence or absence of an inert solvent therefor e.g. aliphatic or aromatic hydrocarbons; it should be noted that hydrogen chloride is given off and a tertiary amino group is formed, which—if desired—may be used for salt formation by using methods known *per se*.

The chloracetic acid ester of α-tocopherol which is used as starting material, may, for example, be produced by using one of the following methods.

a) α-tocopherol and the acid chloride of

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chloracetic acid are heated in an oxygen free atmosphere and in an anhydrous solvent, for example toluene or xylene, e.g. by heating for some time on a water bath in an atmosphere of carbon dioxide or nitrogen;

b) monochloracetic acid (for example in benzene) is boiled with 2,5,6-trimethyl-4-hydroxy-1-phenyldiazoniumchloride, nitrogen being split off and 2,5,6-trimethylhydroquinonemonochloracetate-1 being formed. This compound is dissolved in, e.g. benzene, heated in an oxygen free atmosphere (e.g. in carbon dioxide or nitrogen) with phytol or *iso*phytol and zinc chloride on a water bath. α-tocopherol chloracetic acid ester is formed.

The following examples illustrate the invention without, however, limiting it:—

EXAMPLE 1.

a) 300 g of monochloracetic acid are dissolved in 600 ml of benzene in a three necked flask while heating and stirring. During the heating operation 200 g of moist diazonium salt (2,5,6-trimethyl-4-hydroxy-1-phenyl-diazoniumchloride) are added to the solution and boiling is effected for two hours while stirring and refluxing, nitrogen being formed during this procedure. After cooling the benzene is distilled off at a pressure of approximately 60 mm of Hg followed by removal of excess monochloracetic acid on an oil bath. The residue remaining from distillation is taken up in either and washed with a 1% ammonia solution until neutral. The ether is dried, filtered and distilled off. The residue is stirred with low boiling point range petroleum ether and the resulting crystals (trimethylhydroquinone) are filtered off with suction. The mother liquor is evaporated and distilled in a high vacuum (1.5 mm of Hg, 145—170° C.). 2,5,6-trimethylhydroquinonemonochloracetate-(1) is obtained having a melting point of 116—117° C.

b) 48 g of the chloracetate produced at a) above are dissolved in 200 ml of benzene and stirred with 30 g of phytol or *iso*phytol and 30 g of zinc chloride on a water bath for five hours while bubbling through carbon dioxide. The benzene solution is washed with two portions of 100 ml of water, treated with bleaching powder and distilled off. The residue is mixed with 60 ml of petroleum ether in order to separate out the unreacted chloracetate. After distilling off the petroleum ether in an atmosphere of carbon dioxide there remains α-tocopherol chloracetate in the form of a brown oil. The material is purified by high vacuum distillation (219—230° C., 0.01 mm of Hg). The material is obtained as a light greenish yellow oil which crystallises after standing for some time at a low temperature to form ramiform felted fine needles of α-tocopherol chloracetate crystals.

c) 10 g of the end product of b) above together with 15 ml of diethylamine and 2.5 g of sodium hydrogen carbonate are brought to the boil at reflux for three hours. After the addition of a further 10 ml of diethylamine boiling is continued for two hours. After cooling the material is taken up in ether and the resulting solution is filtered off from excess sodium hydrogen charbonate. The diethylamine is washed away by means of dilute acetic acid, the ether is dried and distilled in an atmosphere of carbon dioxide. The remaining reddish yellow oil is the diethylamino-acetic acid ester of α-tocopherol.

EXAMPLE 2.

50 g of α-tocopherol are dissolved in 200 ml of toluene and 50 g of chloracetic acid chloride are added to this solution. Thereupon the material is warmed on a steam bath at reflux and while stirring for twelve hours. Dry carbon dioxide is bubbled through the resulting solution. The solution is then diluted with an equal amount of toluene and then washed with four portions of 500 ml of a 1% hydrogen carbonate solution. After drying and, if necessary, bleaching the toluene solution, the solvent is removed in a vacuum and the residue distilled subsequently. Reaction with diethylamine is effected in similar manner to that of Example 1, c.)

EXAMPLE 3.

10 g of α-tocopherol monochloracetate, obtained as in Example 1 b) or Example 2, are dissolved in 40 ml of absolute ethanol, 2.5 g of sodium hydrogen carbonate and, over a period of five hours while warming continuously, 100 g of 33% dimethylamine in 4 portions are added. After warming for five hours the excess dimethylamine is distilled off, the residue is taken up in ether and washed several times with 2% acetic acid. After drying and distilling off the ether there remains α-tocopherol dimethylaminoacetate as a yellowish viscous oil.

EXAMPLE 4.

5 g of α-tocopherol diethylaminoacetate are dissolved in 3 ml of absolute ethanol and the solution is made acid with twice normal ethanolic hydrochloric acid solution. After a short time, particularly quickly on standing on ice, tocopherol diethylaminoacetate hydrochloride crystallises out. It is particularly suitable to use the said salt by dissolving the free base in acetone and neutralising with ethanolic solution of hydrochloric acid. Melting point= 156—157° C.

EXAMPLE 5.

On adding aqueous hydrobromic acid solution to a solution in absolute ethanol of α-tocopherol diethylaminoacetate there is formed immediately a crystalline precipitate of α-tocopherol diethylaminoacetate hydrobromide. Melting point=170—171° C.

EXAMPLE 6.

30 g of α-tocopherol dimethylaminoacetate are dissolved in four times the amount of acetone and the resulting solution is made acid by means of an ethereal solution of hydrochloric acid; crystallisation of α-tocopherol dimethylaminoacetate hydrochloride commences immediately. After filtering with suction the material is dissolved in 30 times the amount of acetone and recrystallised. Melting point 192—193° C.

α-tocopherol dimethylaminoacetate hydrobromide is produced in analogous manner. The free base is made acid by means of a 66% aqueous solution of hydrogen bromide. Melting point 202—203.5° C.

30 g of free base are dissolved in four times the amount of acetone and made acid by means of a solution in ethanol of sulphuric acid. α-tocopherol dimethylamino-acetate sulphate precipitates immediately in the form of prisms. The wax-like crystals are recrystallised from acetone, and the substance sinters at 225° C. decomposes at 240° C. with the formation of bubbles.

EXAMPLE 7.

α-tocopherol diethylaminoacetate is taken up in double its weight of acetone and the quantity of tartaric acid theoretically required to produce the tartrate is added thereto. The resulting mixture is warmed until a homogeneous solution is obtained; upon cooling, six volumes of isopropyl ether are added. After standing at ambient temperature the tartaric acid salt of the said base precipitates and is filtered with suction. The said salt is colourless and melts at 170° C. (with decomposition preceded by sintering).

EXAMPLE 8.

The procedure of Example 7 was used to produce the tartaric, citric, phosphoric and sulphuric acid salts of α-tocopherol diethylaminoacetate.

It will be observed that the novel N-dialkylated aminoacetic acid esters of this invention form well defined water soluble salts. Such salts, accordingly, remain stable and soluble in an acid medium; accordingly, the said salts are stable in the stomach juice and acid cell medium of the animal organism.

WHAT WE CLAIM IS:—

1. Dialkylamino-acetic acid esters of α-tocopherol, of which each of the alkyl groups contains 1 or 2 carbon atoms.

2. Physiologically acceptable salts of dialkylaminoacetic acid esters of α-tocopherol, of which each of the alkyl groups contains 1 or 2 carbon atoms.

3. The sulphate of the diethylamino-acetic acid ester of α-tocopherol.

4. The dimethylamino-acetic acid ester of α-tocopherol.

5. The diethylamino-acetic acid ester of α-tocopherol.

6. The hydrobromide of the dimethylamino-acetic acid ester of α-tocopherol.

7. The hydrochloride of the dimethylamino-acetic acid ester of α-tocopherol.

8. The hydrochloride of the diethylamino-acetic acid ester of α-tocopherol.

9. The hydrobromide of the diethylamino-acetic acid ester of α-tocopherol.

10. The tartrate of the dimethylamino-acetic acid ester of α-tocopherol.

11. The sulphate of the dimethylamino-acetic acid ester of α-tocopherol.

12. The citrate of the dimethylamino-acetic acid ester of α-tocopherol.

13. The phosphate of the dimethylamino-acetic acid ester of α-tocopherol.

14. The tartrate of the diethylamino-acetic acid ester of α-tocopherol.

15. The citrate of the diethylamino-acetic acid ester of α-tocopherol.

16. The phosphate of the diethylamino-acetic acid ester of α-tocopherol.

17. A process for the production of dialkylamino-acetic acid esters of α-tocopherol, characterised in that α-tocopherol chloracetic acid ester is reacted with a dialkylamine.

18. A process according to Claim 17, in which the reaction is effected by heating a solution of the starting materials.

19. A process according to either of Claims 7 and 8, in which the α-tocopherol chloracetic acid is produced by heating in an oxygen free atmosphere α-tocopherol and the acid chloride of chloracetic acid in an anhydrous solvent therefor.

20. A process according to either of Claims 17 and 18, in which the α-tocopherol chloracetic acid ester is produced by boiling a solution of monochloracetic acid with 2,5,6-trimethyl-4-hydroxy-1-phenyldiazoniumchloride to form 2,5,6-trimethylhydroquinone-monochloracetate-1, dissolving the last mentioned material in an inert solvent and heating in an oxygen free atmosphere the resulting solution with zinc chloride and phytol or *iso*phytol.

21. A process for the production of dialkylamino-acetic acid esters of α-tocopherol or salts thereof substantially as herein described.

22. A process for the production of dialkylamino-acetic acid esters of α-tocopherol or salts thereof substantially as herein described with reference to any one of the examples.

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